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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,450	09/15/2003	Merja E. Penttila	GC590-2-C1	2737

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EXAMINER	
SCHLAPKOHL, WALTER	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/663,450	PENTTILA ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-13,26-34,36,83-85,87 and 89-98* is/are pending in the application.

4a) Of the above claim(s) *83-85 and 87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5-13,26-34,36 and 89-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/15/2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/15/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of the papers filed 6/16/2006 in which claims 1, 4 and 88 were cancelled, claims 2, 26-27, 29, 36, 89-93 and 95 were amended, and claims 96-98 were added. Claims 1, 4, 14-25, 35, 37-82, 86, and 88 are cancelled. Claims 83-85 and 87 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/17/2005. Claims 2-3, 5-13, 26-34, 36, 83-85, 87, and 89-98 are pending. Claims 2-3, 5-13, 26-34, 36 and 89-98 are under examination in the instant Office action.

Information Disclosure Statement

The examiner has considered the references present in the parent application(s) listed on the information disclosure statement submitted on 9/15/2003. Accordingly, the initialed information disclosure statement is included as part of this Office action.

Specification

Applicant's amendment is found to be remedial in obviating the objection to the specification.

Claim Objections

Applicant's amendment has rendered the objection to claim 1 moot.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1-2, 4, 26-27, 29, 36, 88-90 & 95, and therefore dependent claims 3, 5-13, 28, 30-34 & 91-94,2-3, 5 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is hereby **WITHDRAWN** due to Applicant's amendment.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-3, 5-13, 26-34, 36, 89-90 and 93-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection. This is a new rejection necessitated by Applicant's amendment.**

The specification as originally filed does not provide support for the invention as now claimed: "a nucleic acid encoding the HAC1 UPR-modulating protein comprising a DNA binding domain having at least 90% sequence identity to a DNA binding domain of a) amino acid residues 84-147 of SEQ ID NO: 5; b) amino acid residues 53-116 of SEQ ID NO: 6 or c) amino acid residues 45-116 of SEQ ID NO: 19" (claim 2); "wherein said UPR-modulating protein comprises a DNA binding domain that has at least 90% identity to the DNA binding domain of a)amino acid

residues 84-147 of SEQ ID NO: 5 or b) amino acid residues 53-116 of SEQ ID NO: 6" (claim 89); "wherein said UPR modulating protein comprises a DNA binding domain that has at least 95% identity to the DNA binding domain of a) amino acid residues 84-147 of SEQ ID NO: 5; b) amino acid residues 53-116 of SEQ ID NO: 6 or c) amino acid residues 45-116 of SEQ ID NO: 19" (claim 90); "the UPR-modulating protein comprising a DNA binding domain that has at least 90% identity to the DNA binding domain of a) amino acid residues 84-147 of SEQ ID NO: 5 or b) amino acid residues 53-116 of SEQ ID NO: 6" (claim 95); and "the UPR-modulating protein comprises a DNA binding domain that has at least 95% sequence identity to the DNA binding domain of a) amino acid residues 84-147 of SEQ ID NO: 5 or b) amino acid residues 53-116 of SEQ ID NO: 6" (claims 96-97). The specification does not provide sufficient blazemarks nor direction for the instant nucleic acids encompassed by the above-mentioned limitation, as currently recited. The instant claims now recite a limitation, which was not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as filed. Such a limitation recited in the present claims, which did not appear in the specification as filed, introduces new concepts and violates the description requirement of the first paragraph of 35 U.S.C. 112.

Claims 2-3, 5-13, 26-34, 36 and 89-98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record, but has been extended and slightly altered in order to accommodate Applicant's amendment.**

The claims are drawn to methods of increasing the secretion of a heterologous protein in a eukaryotic cell, said method comprising inducing an unfolded protein response (UPR) by increasing the presence of a HAC1 UPR-modulating protein in the eukaryotic cell, comprising transforming the cell with a nucleic acid encoding the HAC1 UPR-modulating protein. The eukaryotic cell can be transformed with any nucleic acid encoding a HAC1 UPR-modulating protein as long as that protein comprises a DNA binding domain that has at least 90% or 95% sequence identity to a DNA binding domain of a) amino acid residues 84-147 of SEQ ID NO: 5; b) amino acid residues 53-116 of SEQ ID NO: 6 or c) amino acid residues 45-116 of SEQ ID NO: 19, thereby increasing the secretion of the heterologous protein relative to secretion of the heterologous protein in a parental cell. The claims

encompass any HAC1 UPR-modulating protein (including mutants, chimeric proteins, etc.) isolated from any yeast or any filamentous fungi with a DNA binding domain with at least 90% similarity to a DNA binding domain recited in claim 2. Some claims are further limited to such UPR-modulating proteins comprising a DNA binding domain having the DNA binding domain of amino acid residue positions 84 to 147 of SEQ ID NO: 5, wherein said UPR-modulating protein comprises a DNA binding domain having the DNA binding domain of amino acid residue positions 53 to 116 of SEQ ID NO: 6. Some claims are further limited to such a method wherein the heterologous protein is selected from the group consisting of proteases, carbohydrases, reductases, oxidases, isomerases, transferases, kinases, phosphatases, alpha-amylases, glucoamylases, hemicellulases, pectinases and ligninases. The claims do not provide any structural information with regard to the portions of such DNA binding domains which are critical for HAC1 UPR-modulating function. The claims also do not provide any structural information for which recited DNA binding domain-containing sequences would be functional as HAC1 UPR-modulating proteins. The claims also do not provide any structural information with regard to the heterologous proteins whose secretion can be increased by such a method. Thus, the rejected claims comprise a set of nucleic

acid sequences which encode amino acid sequences that are defined by the function of the encoded protein(s).

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of a complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, and any combination thereof. The specification describes HAC1/hacA proteins from four different species of yeast or filamentous fungi: *Saccharomyces cerevisiae, Trichoderma reesei, Aspergillus niger,* and *Aspergillus nidulans*; and the approximate sequences of DNA binding domains for three of the above named species: *T. reesei, A. niger* and *A. nidulans* (see entire document, especially last paragraph on page 19). No description is provided of those residues within the identified DNA binding domains which are essential for DNA binding; neither are any motifs described which would allow one of skill in the art to identify any nucleic acid sequence encoding a HAC1 UPR-modulating proteins with DNA binding domains with even 95% or 100% identity to one of the DNA binding domains recited in claim 2 such that the HAC1 UPR-modulating protein is able to induce an unfolded protein response for any heterologous protein.

Even if one accepts that the examples described in the specification meet the claim limitations of the rejected claims with regard to structure and function, the examples are only representative of four HAC1/hacA UPR-modulating proteins comprising a DNA binding domain as recited in claim 2. The results are not necessarily predictive of any nucleic acid sequences encoding an amino acid sequences comprising a HAC1 UPR-modulating protein comprising a DNA binding domain with 90% identity to a DNA binding domain set forth in claim 2. Thus it is impossible to extrapolate from the examples described herein those amino acid molecules that would necessarily meet the structural/functional characteristics of the rejected claims.

The prior art does not appear to offset the deficiencies of the instant specification in that it does not describe any other UPR-modulating proteins isolated from yeast or filamentous fungi comprising a DNA binding domain set forth in claim 2 or comprising a DNA binding domain with 90% or 95% identity to a DNA binding domain set forth in claim 2. Robinson et al (*Bio/Technology* **12**:381-384, 1994; IDS Ref.) teach that PDI overexpression increases the secretion of heterologous proteins from S. cerevisiae (see entire document, especially the Abstract). However, Robinson et al do not teach that HAC1 or

any other UPR-modulating proteins can also increase the secretion of a heterologous protein.

Given the very large genus of nucleic acids which can encode the amino acid molecules encompassed by the rejected claims, and given the limited description provided by the prior art and specification with regard to the nucleic acid sequences (chimeric, homologous, mutant and otherwise) capable of fulfilling the claim limitations of claims 2-3, 5-13, 26-34, 36 and 89-98, the skilled artisan would not have been able to describe the broadly claimed genus of UPR-modulating proteins isolated from yeast or filamentous fungi comprising a DNA binding domain with at least 90%, 95% or even 100% identity to a DNA binding domain set forth in claim 2 such that an unfolded protein response is induced and such that the secretion of any heterologous protein is increased. Thus, there is no structural/functional basis provided by the prior art or instant specification for one of skill in the art to envision those amino acid sequences that satisfy the functional limitations of the claims. Therefore, the skilled artisan would have reasonably concluded applicants were not in possession of the claimed invention.

Claims 2-3, 5-13, 26-34, 36 and 89-98 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for HAC1/hacA isolated from *S. cerevisciea*, *T. reesei*, and *A. niger var. awamori* used in conjunction with certain secreted heterologous proteins, does not reasonably provide enablement for *A. nidulans* HAC1 or any other HAC1 UPR-modulating protein comprising a DNA binding domain set forth in claim 2 or comprising a DNA binding domain with 90%, 95% or even 100% identity with a DNA binding domain set forth in claim 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record, but has been extended and slightly altered in order to accommodate Applicant's amendment.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The rejected claims are drawn toward a method of increasing the secretion of a heterologous protein in a eukaryotic cell comprising inducing an elevated unfolded protein response (UPR) by transforming the cell with any nucleic acid encoding any HAC1 UPR-modulating protein comprising a DNA binding domain that has at least 90%, 95% or even 100% identity to a DNA binding domain of amino acid residues 84-147 of SEQ ID NO: 5; b) amino acid residues 53-116 of SEQ ID NO: 6; or c) amino acid residues 45-116 of SEQ ID NO: 19, such that the an unfolded protein response is induced and the secretion of the heterologous protein relative to secretion of the heterologous protein in a parental cell is increased. The invention is complex in that it involves the presence of a UPR-modulating protein with the recited limitations, the concurrent heterologous expression of a protein which is secreted and the manipulation of the unfolded protein response such that the secretion of the heterologous protein is increased by increasing the presence of the recited UPR-modulating protein. Increasing the presence of a UPR-modulating protein is not simply a matter of expressing any form of a UPR-modulating protein. For example, endogenous HAC1 protein is only expressed after a 252 nucleotide intron is spliced from the HAC1 mRNA and this requires an unconventional tRNA ligase-dependent pre-mRNA

splicing event (Shamu, C, Splicing: HACking into the unfolded-protein response, Current Biology, 8:R121-R123, 1998; of record; see entire document, especially page R121, third and fourth paragraphs). It further appears that the cell maintains a balance of unspliced and spliced transcripts while undergoing the unfolded protein response and that the primary control of HAC1 function is at the level of translation (see, e.g., Shamu at page R122, paragraph bridging the first and second columns as well as page R123, 3rd full paragraph). Furthermore, this difference in expression/translation between "induced" and "uninduced" forms of the protein is the result of only a few amino acid changes at their respective carboxyl termini (see Shamu at page R123, 3rd paragraph).

Breadth of the claims: The claims are very broad in that they encompass any nucleic acid encoding a HAC1 UPR-modulating protein comprising a DNA binding domain that is 90% similar to a DNA binding domain set forth in claim 2 such that any heterologous protein's secretion is increased.

Guidance of the specification/The existence of working examples: The specification teaches that secretion of a heterologous protein can be increased by expression of a UPR inducing form of a HAC1 recombinant nucleic acid. There are <u>two</u> working examples in the specification of methods for increasing

the secretion of a heterologous protein comprising inducing a UPR by increasing the presence of a UPR-modulating protein isolated from yeast or filamentous fungi: Examples 7 & 9 describe how increased HAC1 isolated from *T. reesei* increases the secretion of heterologous alpha-amylase and chymosin, respectively; Example 12 describes how hacA from *A. niger var. awamori* increases the secretion of heterologous laccase and/or preprochymosin. No specific teachings are provided with regard to inducing other HAC1 UPR-modulating proteins isolated from yeast or filamentous fungi comprising a DNA binding domain with 90%, 95% or even 100% identity to a DNA binding domain set forth in claim 2 wherein the induction of the elevated UPR results in the increased secretion of the heterologous protein.

State of the art: At the time of Applicant's invention, the art of increasing heterologous protein secretion via induction of a HAC1 UPR-modulating protein isolated from yeast or filamentous fungi comprising a DNA binding domain with at least 90%, 95% or even 100% identity to a DNA binding domain set forth in claim 2 was underdeveloped.

Predictability of the art and the amount of experimentation necessary: Clarke et al teach the generation of a reporter gene construct to examine the role of an increase in the IRE1-mediated unfolded protein response on heterologous protein

expression (*J. Cell. Bioch.* Suppl. No 19B, 1995, p.209; of record). However, in an article published post-filing of the instant application Valkonen et al (*Applied and Environmental Microbiology* **69**(4):2065-2072, 2003) teach that overexpression of the yeast HAC1 or *T. reesei* hac1 can lead to increased secretion of heterologous alpha-amylase but not heterologous endoglucanase (see entire document, especially the Abstract and Figures 2B and 4B on pages 2068 and 2070, respectively). Valkonen et al also teach that "we still do not completely understand the features of proteins that affect their secretion and what specific problems different proteins may encounter in heterologous hosts" (page 2071, last paragraph). It is clear that one skilled in the art would be required to conduct a number of experiments to determine which UPR-modulating proteins encompassed by the rejected claims could be used in conjunction with which heterologous proteins in a method to increase heterologous protein secretion in a eukaryotic cell. This unpredictability is exacerbated by the large genus of nucleic acids encoding HAC1 UPR-modulating proteins comprising a DNA binding domain set forth in claim 2 and the almost limitless list of potentially secreted heterologous proteins.

Response to Arguments

Applicant argues that the rejections of the claims under 35 U.S.C. § 112, first paragraph, is rendered moot by the claim amendments. Applicant's argument and amendments have been considered carefully but are respectfully found unpersuasive as the amendments to the claims are not remedial to withdrawn the cited rejections. Examiner's rejections and reasoning are as explained above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1-13, 26-34, 36 and 88-95 under 35 U.S.C. 102(b) as being anticipated by Clarke et al (J. Cell Bioch. Suppl., no 19B, page 209, 1995; of record) as evidenced by Shamu (Current Biology 8:R121-R123, 1998; of record) is hereby **WITHDRAWN**.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax

telephone number for the Group is (571) 273-8300. Note: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should

be directed to Walter Schlapkohl whose telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Thursday from 8:30 AM to 6:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

August 28, 2006

NANCY VOGEL
PRIMARY EXAMINER